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Pharmacokinetic Optimisation of Cancer Chemotherapy

Effect on Outcomes

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Summary

Cancer chemotherapy doses are empirical in that the majority are administered at a fixed dose (mg/m^2 or mg/kg). One reason for this is the intrinsic sensitivity of the tumour or host cells to one particular chemotherapy agent is unknown. Therefore, the likelihood of response or toxicity is unpredictable *a priori*. This contrasts with antimicrobial chemotherapy where sensitivity (minimum inhibitory concentration) can be determined for a specific bacterium. The pharmacokinetics of cancer chemotherapy agents is also highly variable between patients. In addition, the small therapeutic index of these drugs, combined with the lack of good surrogate markers of toxicity or response, adds to the empiricism of the administration of cancer chemotherapy.

In the past few years, numerous studies have established good relationships between systemic exposure to cancer chemotherapy and both response and toxicity. These relationships have been used to individualise chemotherapy dose administration *a priori* and *a posteriori*. Some examples of drugs which are individualised based on their pharmacokinetics are methotrexate, busulfan and carboplatin. Other examples of antineoplastic agents which may eventually be individualised based on their pharmacokinetics are mercaptopurine, fluorouracil, etoposide and teniposide, topotecan and suramin.

New strategies are being investigated to improve the therapeutic index of cancer chemotherapy agents such as biomodulation, pharmacogenetics, circadian administration and the modification of drug scheduling. Pharmacokinetic studies have also played a major role in these areas.

Thus, despite the empiricism associate with cancer chemotherapy administration, some progress has been made and shown to have an impact on outcome. However, more studies are needed to improve cancer chemotherapy administration.

Advances in the field of cancer chemotherapy have led to an increase in the long term survival of patients with malignancies such as acute lymphoblastic leukaemia, testicular cancer and Hodgkin's disease; however, cancer continues to be a major cause of death world-wide.[1]

Improving cancer treatment remains an important challenge. One obvious area of interest is drug development, however, new drug discovery has its limitations. Another area of interest, one which has resulted in the greatest improvement in the outcome of cancer chemotherapy is improving the methods of administering the existing agents. Pharmacokinetic and pharmacodynamic studies have become increasingly important to improve drug delivery strategies.

The impressive cure rate currently achieved in childhood acute lymphoblastic leukaemia represents a major success story in the field of modern cancer treatment.[2] Even though there has been an increase in the incidence of childhood acute lymphoblastic leukaemia, overall mortality has continued to drop because of an improvement in treatment with chemotherapy.[2] For example, in the early 1960s this disease was essentially fatal, whereas the cure rate now approaches 75% overall.[2] Interestingly, the most active drugs used today to treat childhood acute lymphoblastic leukaemia (such as mercaptopurine, methotrexate, prednisone and vincristine) were discovered over 40 years ago.[3,4] Thus, it was by improving the methods of administering these drugs that the treatment outcome was drastically improved.[5] Figure 1 illustrates the improvement in survival rate of children with acute lymphoblastic leukaemia over the past 40 years.

It has been proposed that 4 major criteria must be satisfied for a drug to be considered a good candidate for pharmacokinetic optimisation:[6,7]

- The therapeutic index, or the ratio between the toxic and antitumour drug exposure, must be narrow. If the therapeutic index is large, patients can be treated empirically at therapeutic doses without concerns about toxicity.
- There must be a large degree of interpatient variability, otherwise a fixed dose (mg/m^2 or mg/kg) would produce minimal variations in the plasma concentrations between patients. The degree of intrapatient variability must also be considered. For example, drugs which exhibit a small intrapatient variability (i.e. between treatment cycles) can be adjusted less frequently if their pharmacokinetics are predictable.
- The monitoring of toxic or therapeutic effects must be difficult. If a given drug has a pharmacological effect which is easily monitored its dose can be adjusted based solely on its pharmaco-

cantly reduced the incidence of serious toxicity and essentially eliminated toxic death due to high dose methotrexate.[23,25]

Numerous factors can influence the pharmacokinetics of methotrexate (including age, renal function and hydration) leading to large interpatient variability in the plasma concentrations of methotrexate.[25-27] For example, the same dose of methotrexate (e.g. 1 g/m^2 by continuous intravenous infusion over 24 hours) can produce up to a 7-fold range in drug plasma concentrations.[24] This wide interpatient variability was identified as a cause of treatment failure in patients with childhood acute lymphoblastic leukaemia treated with high dose methotrexate (1 g/m^2).[19] Those with rapid methotrexate clearance had lower steady-state plasma concentrations (C^{ss} <16 μmol/L) and were 3 times more likely to experience any leukaemic relapse compared with patients who had higher plasma concentrations (C^{ss} ≥ 16 μmol/L).[19]

High-dose methotrexate (12 g/m^2 intravenously over 4 hours) is also utilised to treat patients with osteosarcoma. In these protocols, patients with plasma concentrations exceeding 1000 μmol/L at the end of the infusion have a higher probability of achieving a histological response and longer survival than those with concentrations below 1000 μmol/L.[20,21]

Intrathecal methotrexate is very useful for the prophylaxis and treatment of central nervous system (CNS) leukaemia and lymphoma.[28] Although, methotrexate is less neurotoxic than radiotherapy, intrathecal methotrexate has been associated with acute, subacute and chronic neurotoxicity.[29] The pharmacokinetics of methotrexate is highly variable between and within patients when administered by intrathecal or intraventricular injection.[30] Bleyer et al.[31] first showed that methotrexate concentrations in the cerebrospinal fluid were higher in patients who developed neurotoxicity than in patients with CNS leukaemia.

In addition, the volume of cerebrospinal fluid does not increase proportionally with the body surface area.[31] In infants and young children, CNS volume increases more rapidly than the body surface area and the CNS volume of children and adults is equivalent after 3 years of age. Consequently, when the methotrexate intrathecal dose was normalised by body surface area, young patients (i.e. less than 3 years old) were undertreated because of a high volume of cerebrospinal fluid, whereas adult patients were overtreated due to low volumes of cerebrospinal fluid. Because of this, adults experienced greater methotrexate-induced neurotoxicity.

These pharmacokinetic studies led to a methotrexate intrathecal dose nomogram based on patient age which reduces the incidence of methotrexate-induced neurotoxicity and decreases the incidence of CNS relapse.[31] Patients with overt CNS leukaemia in whom methotrexate is administered into the Ommaya reservoir have unpredictable methotrexate concentrations in the cerebrospinal fluid because of the large interpatient and intrapatient variability in the disposition of methotrexate.[30] These patients require lower doses of methotrexate and may require repeated dose administration to maintain cerebrospinal fluid concentrations above the cytotoxic threshold (0.1 μmol/L). Strother et al.[30] have developed a pharmacokinetic methotrexate dose administration regimen in these patients.

At the intracellular level, numerous factors can modulate the methotrexate pharmacological intensity. These processes are:

- transport into the cells by an active membrane transport system with a Michaelis-Menten constant (Km) value of about 5 μmol/L[4,32]
- conversion to more potent methotrexate polyglutamate metabolites by the enzyme folylpolyglutamate synthetase[33]
- gene amplification of the target enzyme dihydrofolate reductase.[4]

All of these processes are possible mechanisms of methotrexate resistance. Whithead et al.[34] first showed that the amount of methotrexate polyglutamate metabolites formed in blast cells was a significant determinant of survival in patients with childhood acute lymphoblastic leukaemia.

Despite evidence demonstrating that higher plasma concentrations produce greater antitumour

effect in both osteosarcoma and childhood acute lymphoblastic leukaemia, some have argued that higher doses of methotrexate were not superior to standard low doses because of the saturable transport system at the membrane level.[32,35,36] To address this issue, a large prospective randomised trial was recently conducted at St. Jude Children's Research Hospital (Memphis, USA), comparing the extracellular and intracellular pharmacology of methotrexate after conventional low dose oral administration or intravenous high dose methotrexate.[24,37] 150 patients with newly diagnosed childhood acute lymphoblastic leukaemia were randomised to receive either low dose fractionated methotrexate orally (180 mg/m^2) or high dose methotrexate (1 g/m^2) intravenously over 24 hours; these doses were selected *a priori* to achieve a steady-state plasma concentrations of 1.0 and 10 μmol/L, respectively. Indeed, plasma concentrations with low dose methotrexate were 0.9 μmol/L on average compared with 12.2 μmol/L for the high-dose arm.[37] Even though the extracellular pharmacokinetics were highly variable, the high dose methotrexate arm achieved greater intracellular methotrexate polyglutamate concentrations which led to greater antileukaemic effects: inhibition of *de novo* purine synthesis and decrease in peripheral blasts.[24,37]

In addition, a subgroup analysis also showed that patients who had B-lineage and hyperdiploid leukaemic cells achieved higher concentration of methotrexate polyglutamate metabolites in leukaemic cells compared with patients with T-lineage and nonhyperdipliod acute lymphoblastic leukaemia.[24,37] These findings were also consistent with the better prognosis observed in patients with B-lineage and hyperdiploid acute lymphoblastic leukaemia.[2,38] This suggests that increased plasma concentrations of methotrexate can overcome, at least partially, the inherent resistance seen at the intracellular level. Even though no prospective dose adjustments were made in this trial, methotrexate toxicity correlated better with methotrexate plasma concentrations than with methotrexate dose, reinforcing the rationale for monitoring methotrexate concentrations to adjust leucovorin rescue. Future studies should define whether higher extracellular concentrations of methotrexate (greater then 10 to 20 μmol/L) will achieve greater benefits in this disease.

2.2 Carboplatin

Carboplatin is an analogue of cisplatin with a different toxicity profile. Unlike cisplatin, which causes nausea and vomiting acutely and ototoxicity and nephrotoxicity chronically, the major dose limiting toxicity of carboplatin is thrombocytopenia.

Carboplatin is excreted renally, almost entirely by glomerular filtration, and therefore a large degree of interpatient variability in the pharmacokinetics of carboplatin can be expected because of the variability in renal function. Various strategies have been developed to estimate carboplatin doses based on renal function among patients.[39-42] Egorin et al.[40] have developed a nomogram in which the carboplatin dose is adjusted based on the patient's body surface area, creatinine clearance and the targeted degree of thrombocytopenia.[40] Another nomogram was developed by Calvert et al.[39] in which the carboplatin dose is adjusted based on glomerular filtration rates as measured by a radioisotope method. Both methods are useful in minimising pharmacokinetic variability and toxicity.

More recently, a population analysis of carboplatin pharmacokinetics was performed to identify physiological characteristics predictive of carboplatin pharmacokinetics.[42] An equation which utilises patient bodyweight, age, gender and serum creatinine was derived to estimate carboplatin clearance in L/h. This formula can predict carboplatin clearance with good precision and minimal bias without having to measure glomerular filtration rates by a radioisotope, in addition to avoiding the drawbacks of urine collection.[42]

A large retrospective database analysis in more than 1000 patients with ovarian cancer[43] examined the relationships between carboplatin systemic exposure (AUC) and toxicity, as well as antitumour

subsequent study, the authors tested a refined model which took in consideration etoposide protein binding and found that prospective pharmacokinetic monitoring allows an increase in dose intensity without a parallel increase in toxicity.[69]

3.4.2 Teniposide

Teniposide is a drug used almost exclusively for the treatment of childhood acute lymphoblastic leukaemia. Like etoposide, teniposide is also metabolised by CYP3A4 but is primarily excreted in the bile.[70,71] Rodman et al.[72] reported a strong correlation between the antileukaemic response and gastrointestinal toxicity and systemic exposure (AUC) of teniposide, but no significant relationships with teniposide doses.

3.5 Topotecan

Topotecan is an analogue of the plant alkaloid 20 *S*-camptothecin, the prototypical DNA topoisomerase I interactive agent.[73] The drug has been recently approved by the US Food and Drug Administration for the treatment of refractory ovarian cancer. However, several studies are underway to evaluate its efficacy in various tumour types (e.g. small-cell lung cancer or leukaemias).

The urinary recovery of topotecan ranges from 40 to 70%, suggesting renal excretion as the primary clearance pathway.[74,75] A recent study performed in patients with normal and impaired renal function reported reduced topotecan clearance in patients with moderate renal dysfunction (i.e. creatinine clearance less than 2.4 L/h).[76] In addition, the study concluded that dosage reductions are required in patients with moderate but not mild renal dysfunction.[76]

In contrast, a paediatric study evaluating topotecan pharmacokinetics in patients with altered and normal renal function suggested that topotecan undergoes elimination from the body by hepatic metabolism, biliary secretion and renal tubular secretion, in addition to glomerular filtration.[77] Moreover, the study suggests that the glomerular filtration rate may not be limiting for topotecan clearance, and in patients with a decrease in glomerular filtration rate the topotecan dose may not need to be reduced due to sufficient clearance by other mechanisms. A recent phase I study of topotecan in patients with normal and hepatic dysfunction reported no differences in the pharmacokinetics or maximum tolerated dose of topotecan in patients with hepatic impairment.[78] Topotecan pharmacokinetics within patients remain relatively constant, but are highly variable between patients.[79]

Evaluation of topotecan pharmacokinetics and pharmacodynamic relationships are complex secondary to topotecan undergoing reversible pH-dependent hydrolysis between the active (lactone) form and the inactive (hydroxy acid) form.[73,80] The lactone ring predominates at acidic pH, whereas hydroxy acid predominates at physiological pH.[81] In addition, plasma pH, protein binding and route of administration may affect the lactone to total (sum of lactone and hydroxy acid) ratio.[81,82]

In vitro studies report 30 to 40% of topotecan in the lactone form at physiological pH (i.e. 7.4),[81] whereas in clinical studies the percentage has varied from 30 to 70%.[74,77,79,83-85] Thus, measurement of lactone systemic exposure may be more important to the overall understanding of topotecan pharmacodynamics (e.g. toxicity or efficacy).

Several adult and paediatric studies have evaluated topotecan pharmacodynamics following a variety of dose schedules and routes of administration. Pharmacodynamic relationships between the primary dose limiting toxicities of neutropenia and thrombocytopenia and topotecan total and lactone systemic exposure have been reported after continuous and daily short infusions.[77,83-85] In a phase I study of maximum tolerated systemic exposure in children with recurrent leukaemia, topotecan was administered as a 120-hour continuous infusion with doses escalated to attain a desired level of systemic exposure.[84] A significant relationship between topotecan lactone systemic exposure and the grade of mucositis was observed. Moreover, a statistically significant mathematical relationship was reported between the proportion of courses with oncolytic effect, as well as mucosal toxicity

and topotecan lactone systemic exposure as shown in figure 3.[84]

The results of preclinical studies conducted at St. Jude Children's Research Hospital (Memphis, USA) suggest that the topotecan antitumour activity is highly schedule dependent, with the greatest antitumour response occurring with protracted regimens achieving an exposure-duration threshold, defined as the maintenance of a concentration or level of exposure (AUC) for a specific period of time.[86,87] In addition, clinical studies described above suggest differences in the level of topotecan systemic exposure producing toxicity and antitumour effect. Although conclusive studies defining the therapeutic index remain to be conducted, topotecan may be an ideal chemotherapeutic agent in which dose administration based on systemic exposure or exposure-duration threshold optimises therapeutic effect.

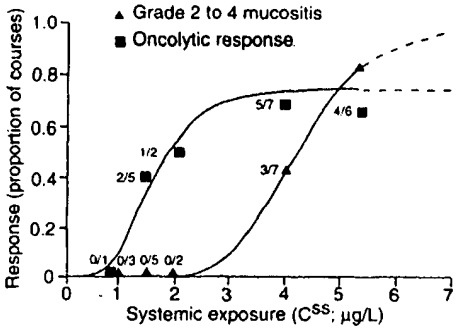

Fig. 3. Plot of topotecan lactone systemic exposure (C^{ss}; µg/L) *vs proportion of courses of therapy with either an oncolytic response or grade 2 to 4 mucositis.* 12 courses of topotecan were associated with an oncolytic response, defined as > 75% reduction in circulating blast count or a complete or partial response based on bone marrow aspirate. The number of courses associated with a response or mucositis is shown in the numerator over the total number of courses at each level of systemic exposure (reproduced from Furman et al.,[84] with permission).

4. Strategies to Improve Therapeutic Index of Antineoplastic Agents

Dose administration strategies that have been shown to improve the outcome of cancer chemotherapy are displayed in table III.

4.1 Dose Adjustment *A Priori*

Knowledge and use of pharmacokinetics to optimise dose administration is used routinely for many different classes of chemotherapy agents. There are numerous examples of drugs for which good relationships between a physiological variable (e.g. serum creatinine and serum albumin) and pharmacokinetic parameters have been identified. With such relationships dose decisions are often made *a priori* based on patient-specific parameters. One limitation to this strategy is that the degree of intrapatient variability should be modest. Otherwise, modification in dosage has to be performed during the course of therapy. Usually the guidelines for dose adjustment are empirical (e.g. a dose reduction of 25% if the serum bilirubin is 1.5 to 3.0 mg/dl for a drug which is excreted in the bile), and in some cases no recommendations exist other than the statement that the dose should be reduced in the face of a given degree of organ dysfunction.

Predicting the pharmacokinetics of certain cancer chemotherapeutic agents using physiological or demographic variables has already proven helpful in reducing interpatient variability and improving therapeutic indices. The best example of *a priori* dose adjustment of an anticancer agent is carboplatin. Calvert et al.[39] first demonstrated that carboplatin AUC could be accurately predicted using an equation which takes into account the patient's pretreatment renal function. This *a priori* method for carboplatin dose administration has led to a substantial reduction in the pharmacokinetic variability, such that carboplatin is currently one of the few drugs which is routinely administered to achieve a target exposure rather than on a mg/m^2 or mg/kg basis.

The rationale for reducing the dose in the presence of renal impairment is well documented for chemotherapeutic agents excreted primarily in urine such as methotrexate, cisplatin, etoposide and bleomycin.[88] However, the majority of chemotherapy agents are extensively metabolised by the liver and dose adjustment is often largely empirical

ible for the methylation of mercaptopurine, a pathway thought to be inactivating, even though this remains controversial.[31] The enzyme activity of thiopurine methyltransferase can be measured in red blood cells and is shown to predict mercaptopurine toxicity.[13,57] Approximately 10% of the population is partially deficient in this enzyme and 1% is completely deficient.[31]

Patients who have complete (homozygote) thiopurine methyltransferase deficiency experience severe myelosuppression following standard mercaptopurine administration.[13,98] By knowing thiopurine methyltransferase status, it could be possible to adjust the dose before the occurrence of serious toxicity. A recent study demonstrated that the activity of this enzyme measured in red blood cells was correlated with the activity measured in lymphoblasts.[56]

Another drug influenced by pharmacogenetic variability is amonafide, a drug which is not currently approved in the US. The drug undergoes acetylation by *N*-acetyltransferase, an enzyme which is polymorphic in humans.[93] Ratain and his group have shown that fast acetylator (36% of the population) experienced significantly more toxicity (i.e. myelosuppression) than slow acetylators.[99,100]

Many chemotherapy agents are extensively metabolised by CYP enzymes, specifically the isoenzyme CYP3A4, as shown in table IV.[101,102] Even though there is no evidence of polymorphism in the phenotype or genotype of this isoenzyme, there is a large degree of interpatient variability in the activity of this enzyme in humans (i.e. up to 6-fold).[1103] Recently, *in vivo* probes have been developed to assess the activity of CYP activities in humans.[1102] For example, the erythromycin breath test was used to adjust cyclosporin (a drug metabolised by CYP3A4) in heart and kidney transplant patients.[1103,1104] Studies are needed to determine whether these tests could adequately predict the pharmacokinetics of the antineoplastic agents listed in table IV.

4.4 Dose Administration Based on Circadian Rhythm

Small modifications in scheduling, such as administration at certain times of the day, have been tested to improve the therapeutic index of antineoplastic agents.[1105] For example, Rivard et al.[1106,1107] demonstrated a significant improvement in survival for children with acute lymphoblastic leukaemia who were receiving mercaptopurine in the evening compared with those who received the drug in the morning. Other chemotherapy agents influenced by circadian rhythm include carboplatin, fluorouracil and busulfan.[1105]

The mechanism by which chemotherapy agents are more effective at certain times of the day is unknown but pharmacokinetic, as well as pharmacodynamic, reasons have been proposed.[1105] One possible explanation is that haemapoiesis is circadian dependent.[1108] Since myelosuppression is the dose-limiting toxicity of a majority of antineoplastic agents, this could explain why administering chemotherapy at a certain period of the day may minimise toxicity and improve outcome. On the other hand, others have also shown that plasma concentrations of antineoplastic agents fluctuate in a circadian manner.[196] Thus, both pharmacokinetics and pharmacodynamics are modified by circadian strategies.

4.5 Biomodulation

The use of biomodulators to increase the therapeutic index of chemotherapy has made a significant impact on certain diseases. A list of cancer

Table IV. Anticancer agents metabolised by cytochrome P450 (CYP) 3A4[70,101,102,129,134,135]

Etoposide
Teniposide
Ifosfamide
Cyclophosphamide
Paclitaxel
Docetaxel
Vincristine
Vinblastine
Vinorelbine

Table V. Biomodulating agents approved for clinical use in combination with cancer chemotherapy

Biomodulator	Chemotherapy agent	Effect
Leucovorin	Fluorouracil	Enhance cytotoxicity to tumour cells
Leucovorin	Methotrexate	Decrease toxicity to normal tissues
Levamisole	Fluorouracil	Increase fluorouracil effectiveness via immunomodulation in patients with colon cancer stage III (Duke)
Amifostine	Cisplatin	Reduce myelosuppression, nephrotoxicity and neurotoxicity[a]
Dexrazoxane (ICRF-187)	Anthracyclines	Decrease anthracycline-induced cardiotoxicity
Mesna	Ifosfamide/cyclophosphamide	Decrease haemorrhagic cystitis
Haematopoietic growth factors: G-CSF, GM-CSF, erythropoietin	Chemotherapy-induced myelosuppression	Decrease chemotherapy-induced neutropenia and anaemia

a Approved indications vary in different countries.

Abbreviations: 5FU = fluorouracil; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte macrophage colony-stimulating factor.

chemotherapy biomodulators approved for clinical use in humans is displayed in table V. These agents can modulate cancer chemotherapy through pharmacokinetic and/or pharmacodynamic modulations.

One of the most widely used biomodulator is leucovorin or 5-formyl tetrahydrofolate. This reduced folate is used in combination with 2 antineoplastic drugs, methotrexate and fluorouracil. Its use with methotrexate decreases toxicity, allowing the escalution of methotrexate doses, up to 33 g/m^2.[125] On the other hand, leucovorin increases fluorouracil cytotoxicity by sustaining the inhibition on thymidylate synthetase.[109] Leucovorin does not affect methotrexate or fluorouracil plasma concentrations. Thus, the biomodulation takes place at the pharmacodynamic level.

Fluorouracil has been administered in combination with dipyridamole based on *in vitro* synergy.[110] However, clinical trials in humans did not show an improvement in fluorouracil therapeutic index when combined with dipyridamole.[111] When the dose-effect relationship was examined in humans, no pharmacological interaction between dipyridamole and fluorouracil could be seen. However, pharmacokinetic and pharmacodynamic analysis revealed that dipyridamole increases fluorouracil clearance, resulting in lower fluorouracil plasma concentrations, but also increases its toxicity by shifting the effect-concentration curve to the left [lower concentration of drug that inhibits activity by 50% (IC_{50})].[112,113] Thus, dipyridamole modulated the pharmacokinetics as well as the pharmacodynamics of fluorouracil such that it did not improve its therapeutic index.[111]

Recently, a potent inhibitor of dihydropyridine dehydrogenase enzyme was found, 5-ethynyluracil (776C85).[114] This compound inhibit dihydropyridine dehydrogenase activity by up to 96% in rat and mouse liver extracts after oral absorption.[114] A phase I study in humans using 5-ethynyluacil with oral fluorouracil has been completed and published recently.[115] It was shown that oral doses of ethynyluracil 10mg twice daily completely inhibited dihydropyridine dehydrogenase activity allowing doses of fluorouracil as low as 1 to 2mg to be administered orally with similar plasma concentrations as those seen with fluorouracil protracted infusion.[115] However, this approach is still in its infancy and more studies are needed to determine if this approach could improve the therapeutic index of fluorouracil.

P-glycoprotein is a 170 kD membrane protein encoded by the multidrug resistance gene (MDR1).[116] The role of this energy-dependent efflux protein is to secrete lipophilic xenobiotic outside the cells.[117,118] This has been designated as the multidrug resistance gene because many cancer chemotherapy agents show crossresistance in tumour cells expressing high levels of P-glycoprotein, such as anthracyclines, vinca alcaloids and taxoids.[116] P-glycoprotein blocking agents have

- delayed and unpredictable pharmacological effects
- better relationship between drug exposure than dose and pharmacological intensity.

Improvements in outcome have been observed using pharmacokinetic principles to individualise cancer chemotherapy administration for some chemotherapy agents (methotrexate, carboplatin and busulfan). Incorporating pharmacokinetics and pharmacodynamics in drug development and clinical trials is essential to maximise the clinical potentials of new antineoplastic agents.

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